

#### IV. REMARKS

##### A. Claim Amendments

Applicants express their appreciation to the Examiners for granting telephone interviews on December 31, 2003, January 22 and February 11, 2004.

As summarized in Applicants' Substance of Interviews filed in the U.S. Patent and Trademark Office on February 11, 2004, the Examiner indicated on January 22, 2004 that claims 1, 15, 41, and 42 as amended herein would be allowable. Applicants' new claims 55-59 are patterned on claims 1, 15, 41 and 42, and therefore are also in condition for allowance. The written description and enablement for the amended claims 1, 15, 41 and 42 and the new claims 55-59 is found in the specification, considered as a whole, e.g., examples 4-6 and 8-11, and the figures, such as Figs. 5-7, 13-15, and 17-20.

New claims 60-63 are substantially the same as indicated by the Examiner in the December 31, 2003 interview that would be allowable. They are also described and enabled by the specification considered in its entirety, including the aforementioned portions thereof. New claim 64 is similarly supported by the specification, considered as a whole, including the figures.

Entry of the new claims and examination thereof on the merits together with all other pending claims is requested. Upon entry of the amendments and new claims in this paper, the following claims will be pending in the application: 1, 5, 6, 8, 11-15, 19, 20, 22, 23, 25-29, 34-36, 39-43, 45, 47-64. Of the pending claims, the following claims will be withdrawn: 6, 8, 11, 12, 20, 22, 23, 25, 26, 43, 45, 47-50, 53, 54.

It is submitted that all claims are in condition for allowance, an indication of which is solicited.

**B. Specification Amendments**

Applicants amended their specification to add a description of various aspects of their invention present in other parts of the original application as filed. Thus, the amendments find written description and enablement in the original application, as filed, considered as a whole, e.g., in the original claims 1-11, 15, 16 and 27 and the Examples.

**C. Listing of the Claims**

It was indicated in the Office Action that status of some of the claims was not correctly indicated, in the Corrected Preliminary Amendment filed on February 24, 2004, and the Amendment filed July 11, 2003. Office Action pp. 2 and 3. Applicants appreciate the Examiner's careful review of the Amendments and bringing to the Applicants' attention the aforementioned informalities. Applicants also express their appreciation to the Examiner for not mailing a notice of non-compliance to expedite prosecution. Applicants have now correctly identified the status of all claims.

**D. Election/Restriction**

It was stated that claims 43-50, 53 and 54 were directed to a non-elected invention, and therefore they were withdrawn from consideration. Applicants agree, and this is reflected in the enclosed claims set.

**E. Information Disclosure Statements**

Applicants appreciate the Examiner's consideration of the Information Disclosure Statement ("IDS") filed on June 28, 2002 and the enclosure with the June 2, 2004 Office Action of the initialed copy of Form PTO-1449.

In the Office Action, it was also indicated that the IDS attached to the Amendment filed by Applicants on July 11, 2003<sup>1</sup>, had not been received. Applicants

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<sup>1</sup> The Office Action referred to an Amendment filed on July 16, 2003. This appears to be a typographical error.

enclose herewith, in Appendix A, a copy of the July 11, 2003, IDS including the listed documents and a copy of the date-stamped postcard indicating receipt thereof by the U.S. Patent and Trademark Office ("USPTO").

Additionally, Applicants also respectfully point out that they filed the following IDSs which have not been acknowledged:

1. Information Disclosure Statement filed March 27, 2001;
2. Supplemental Information Disclosure Statement filed June 26, 2001;
3. Supplement Information Disclosure Statement, filed on August 21, 2001;
4. Supplemental Information Disclosure Statement, filed July 30, 2003;
5. Second Supplemental Information Disclosure Statement, filed on January 2, 2004.

All five IDSs are also collectively referred to herein as "Statements". Please note that in the July 30, 2003 Supplemental Information disclosure Statement, items 4, 5 and 6 (on the Form PTO/SB/08A) are Abstracts (CA) of the respective publications, as identified in the Standard Search Report, (item 3).

For the Examiner's convenience, Applicants enclose copies of the above-identified Statements 1-5, including copies of the references, and date-stamped post cards or certificates of mailing indicating filing of the Statements on the respective dates (see Appendices B-F).

Applicants request consideration of all of these IDSs (copies of which are enclosed in Appendices A-F) and indication thereof by forwarding to Applicants a copy of each form PTO-1449 or its equivalent with the Examiner's initials in the left column per MPEP § 609.

#### F. June 2 and July 2, 2004 Office Actions

Applicants received the July 2, 2004 Office Action pursuant to the Applicants' telephone call, as summarized in the Telephone Interview, attached to the July 2<sup>nd</sup>

Office Action. Applicants appreciate the Examiner's indication in a telephone call on July 15, 2004 that the July 2<sup>nd</sup> Office Action superceded the June 2, 2004 Office Action, and that the period for response is set from the July 2<sup>nd</sup> Office Action.

**G. Claims Rejected**

At the outset, Applicants appreciate the Examiner's indication that the issues relating to enablement have been "greatly simplified during prosecution through multiple interviews." Office Action, p. 4. The interviews were summarized in the Substance of Interviews Under 37 C.F.R. §1.133, filed on February 11, 2004. Applicants agree with the Examiner's assessment and express their appreciation to Examiners Rawlings, Caputa and Eyler for their thoughtful attention to this application.

Claims 1, 5, 13-15, 19, 27-29, 34-36, 39-42, 51 and 52 were rejected under 35 U.S.C., 112, first paragraph, allegedly for containing subject matter not described in the specification in a way to enable persons skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention. It was stated that claims 1, 5, 13, 14, 28, 29, 34-36, 39-41, 51 and 52 were drawn to a method for determining whether an individual is likely to have colorectal cancer, and claims 15, 19, 27, 34-36 and 42 to a method for determining if a patient previously treated for primary breast cancer is likely have metastatic breast cancer.<sup>2</sup> Office Action, p. 4.

In the Office Action it was also asserted that the recitation of "a discriminating value" in the claims would require the practitioner to perform an undue amount of additional experimentation for the reasons addressed in the July 2, 2002, Office Action. It was further asserted that the amount of guidance, direction and exemplification disclosed in the specification was insufficient to meet the enablement requirement of Section 112, first paragraph. Applicants' traversal of this rejection, in the Amendment under 37 C.F.R. § 1.116, filed on July 11, 2003, was characterized as, in essence,

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<sup>2</sup> Applicants respectfully point out that some of these enumerated claims are directed to both methods. For example, claims 13, 14, 34-36, 51 and 52 are directed to both methods.

being "the discriminating value can be easily determined by a clinician based on his or her choice of selectivity and specificity". Office Action, pp. 4-5.

While Applicants agree that the quoted language was their conclusion, they respectfully point out that it was preceded in the July 11, 2003 Amendment by a detailed discussion, spanning almost three pages, describing in detail how a person of ordinary skill in the art, familiar with Applicants' specification would be enabled to practice the full scope of the claimed invention. A similar discussion had taken place at the interview, granted to Applicants on June 25, 2003, and the Examiners agreed that the explanation, together with the amendments agreed to at the interview (reflected in the July 11, 2003 Amendment), would overcome the enablement rejection. E.g., see pp. 13 and 22 of the July 11, 2003 Amendment.

It was also stated in the Office Action that because there is an overlap in the range of the concentrations of TIMP-1 in the bodily fluid of patients known to have cancer with the range of the values of the concentrations of TIMP-1 in the bodily fluids of individuals considered healthy and disease-free, the discriminatory value of TIMP-1 is obscured. Office Action, p. 5. This assertion was also discussed in detail at the June 25, 2003 interview and in the July 11, 2003 Amendment, and it was Applicants' understanding (based on the interview) that they effectively rebutted it.

Finally, in support of the alleged lack of enablement rejection, it was stated that claims 1 and 15 were not enabled because there is insufficient guidance, direction and exemplification in the specification to enable the skilled artisan to determine the likelihood that an individual is pre-disposed to colorectal or malignant breast cancer. Office Action, p. 6.

For all of the reasons discussed at the June 25, 2003 interview and subsequent Amendments, incorporated herein by reference, Applicants continue to assert that the claims at issue, prior to their amendment herein, were fully enabled by the specification. Nonetheless, in the interest of expediting prosecution, Applicants have amended the claims in the manner that the Examiners indicated in the interviews on December 31,

2003, January 12 and 22, 2004, would place them in condition for allowance. Applicants respectfully submit that their claim amendments are not to be interpreted as narrowing the scope of the claims, and they do not intend the amendments to suggest that the claims should be interpreted to have a scope other than the full open-ended scope thereof required by their terminology.

**H. The Claims Were Definite Prior to the Amendment Herein; the Amended Claims Continue to be Definite.**

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Claims 1, 5, 13-15, 19, 27-29, 34-36, 39-42, 51 and 52 were rejected under 35 U.S.C. 112, 2<sup>nd</sup> paragraph, as indefinite. It was stated that claim 13 was indefinite because of the recitation "wherein the individual is a member of an unselected population". The basis for this rejection was that if an individual is screened using the method of claim 1, he would be a member of a selected population. Therefore, allegedly, one could not determine how to practice the method with a member of an unselected population, thereby making it impossible to determine the metes and bounds of the claimed subject matter. Office Action, p. 7. Applicants respectfully disagree. It is well established that definiteness of a claim must be considered in view of the specification. In their specification, Applicants set forth a distinction between an "unselected population" and a population "already identified as having an increased risk of developing cancer. . ." See p. 5, lines 12-19. Thus, claim 13, prior to its amendment herein was definite. Nonetheless, to expedite prosecution of the application, Applicants amended that claim, consistent with the specification. The amended claim 13 continues to be definite.

Claims 1, 4, 5, 13-15, 18, 19, 27-36 and 38-42 were characterized as being vague and indefinite due to the recitation of "a discriminating value".

As discussed above, Applicants have traversed rejections based on that recitation before, and they continue to do so. Nonetheless, in the interest of expediting prosecution and consistent with agreements reached during the interviews discussed above, the relevant claims have been amended, and they continue to be definite.

With respect to these, and any other claim amendments, Applicants respectfully submit that the scope of their amended claims was not narrowed, and the amended claims continue to have a scope defined by their open-ended terminology.

**I. Holten-Andersen *et al.* (1999) Is Not Prior Art to Applicants' Claimed Invention. Rejection in View of This Reference is Misplaced.**

Holten-Andersen *et al.* "Quantitation of TIMP-1 in plasma of healthy blood donors and patients with advanced cancer", *British Journal of Cancer*, 80:495-503, 1999 ("Holten-Andersen (1999)"), was the basis for rejecting claims 1, 15, 34, 35, 39 and 40 as anticipated under 35 U.S.C. § 102(a) and claims 1, 14, 51 and 52 as obvious under 35 U.S.C. § 103(a). Pages 7-8 of the Office Action.

Applicants respectfully submit that this rejection is misplaced because Holten-Andersen (1999) is not prior art to their claimed invention since the reference was published in May 1999, as indicated by the attached printout from the British Journal of Cancer website (see Tab 1, which also includes a copy of Holten-Andersen (1999)). Applicants' application was filed in the USPTO on April 10, 2000 and it claims priority under 35 U.S.C. § 119 from Denmark Patent Application 1999 00476, filed on April 9, 1999. (A Certified copy of the Danish priority application was filed on June 26, 2001. Also, see the filing receipt mailed on June 13, 2000 and the Office Action Summary of November 9, 2001, indicating that certified copies of the priority documents had been received.) Since Applicants' U.S. application was filed on April 10, 2000, Holten-Andersen (1999) is not prior art under 35 U.S.C. § 102(b), because it was published less than one year prior to the Applicants' filing date. Further, the April 9, 1999 priority date of this application antedates the May 1999 publication of Holten-Andersen (1999). Thus, the reference is not prior art with respect to Applicants' claims. See 35 U.S.C. § 119(a). Accordingly, the withdrawal of anticipation and obviousness rejections over this reference is respectfully requested.

J. **The Double-Patenting Rejection Is Misplaced. Applicants Request Holding This Rejection In Abeyance Until All Other Issues Are Resolved.**

All claims examined on the merits were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as unpatentable over claims 1-12, 26-29, 33-35 and 37-45 of co-pending Application No. 10/117,030 (hereinafter also referred to as the “030 application”). It was stated that, while the conflicting claims are not identical, they are patentably indistinct from each other because the claims in this application and the co-pending claims are directed to the same or nearly the same methods of screening an individual to determine if he has colorectal cancer or malignant breast cancer. Office Action, p. 9.

At the outset, Applicants respectfully point out that the claims examined in this application and the aforementioned claims in the ‘030 application are not directed to the same patentable invention, but in fact are directed to different patentable inventions. For example, Claim 1 in the instant application is directed to a method for screening an individual for colorectal cancer by measuring a total concentration of TIMP-1 in a plasma sample of the individual and comparing it to the total plasma TIMP-1 concentration value corresponding to a determined specificity. In contrast, claim 1, for example, in the ‘030 application is directed to a method for determining whether an individual is likely to have minimal residual disease, recurrent cancer or a combination thereof, after being treated for the primary cancer, comprising determining at least one first parameter representing a post-operative concentration of TIMP-1 in body fluid samples and comparing it to a discriminating value to determine the likelihood of that individual having minimal residual disease, recurrent cancer or a combination thereof. The invention of Applicants’ claim 1 would not have been rendered obvious by the claims in the ‘030 application. Other differences exist between the claims in this application and the co-pending claims in the ‘030 application. Applicants reserve their right to discuss in detail all the differences between the two sets of claims at an appropriate time.

Nonetheless, even if, *arguendo*, the provisional double-patenting rejection were proper, Applicants respectfully request that this rejection be held in abeyance until such time as all other issues are resolved in this application at which time procedure outlined in the MPEP § 804 should be followed, i.e., the double-patenting rejection should be withdrawn and the application permitted to issue as a patent, providing other conditions of that section are satisfied. See the MPEP, pp. 800-19.

**K. Commonly Assigned '030 Application Would Not Form The Basis For A Rejection Under 35 U.S.C. § 103(a) Because It Fails To Establish Knowledge Of Applicants' Claimed Invention By Others Prior To The Time Applicants Made It.**

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It was stated that the claims examined in the application (claims 1, 5, 13-15, 19, 27-29, 34-36, 39-42, 51 and 52) are directed to an invention not patentably distinct from claims 1-12, 26-29, 33-35 and 37-45 of the commonly assigned '030 application. Substantially the same reasoning which was applied to the provisional double-patenting rejection was relied upon for this assertion. Office Action, pp. 9-10.

It was further asserted that the '030 application "would form the basis for a rejection of the noted claims under 35 U.S.C. § 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made." Office Action, p. 10. The assignee was required under 35 U.S.C. § 103(c) ("Section 103(c)") and 37 C.F.R. § 1.78(c) to:

1. show that the conflicting inventions were commonly owned at the time the invention in this application was made; or
2. name the prior inventor of the conflicting subject matter.

It was further stated that the failure to comply with this requirement would result in abandonment of the application. *Id.*

Applicants respectfully traverse this assertion. At the outset, as discussed above, Applicants respectfully submit that claims examined in this application are

directed to an invention which is patentably distinct from the identified claims of the co-pending '030 application. Therefore, the inventions are not conflicting. Furthermore, Section 103(c) must be examined in the context of Section 103(a) which states, in pertinent part "A patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious ..." Applicants respectfully point out that the co-pending '030 application is not prior art to Applicants' invention claimed herein at least because the filing or priority dates of the '030 application do not pre-date Applicants' filing or priority dates.

The improper nature of this requirement is underscored by 37 C.F.R. § 1.78(c) which states, in pertinent part

"... if an application ... and at least one other application naming different inventors are owned by the same party and contain conflicting claims, and there is no statement of record indicating that the claimed inventions were commonly owned or subject to an obligation of assignment to the same person at the time the later invention was made, the Office may require the assignee to state whether the claimed inventions were commonly owned or subject to an obligation of assignment to the same person at the time the later invention was made ... ."

Thus, the two applications need to have conflicting claims, and the inventions need to be commonly owned or subject to an obligation of common ownership at the time the later invention was made (in this instance the invention of the '030 application, based on the facts of record in this and the '030 application). There are no conflicting claims between the two applications. Also, the statement is required with respect to the "later invention", not an earlier one as stated in the Office Action.

For at least these reasons, the requirement is misplaced.

Nonetheless, in the interest of expediting prosecution, Applicants plan to submit a statement, pursuant to 37 C.F.R. § 1.78(c), by an appropriate person that the inventions of this application and of the '030 application were commonly owned or

subject to an obligation of assignment to the same person at the time the invention of the '030 application was made.

**L. References Enclosed With the Office Action.**

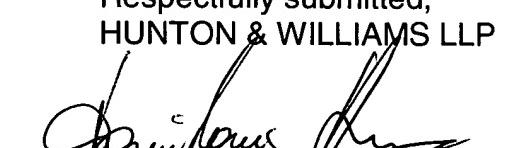
Applicants note two references enclosed with the Office Action, Holten-Andersen MN, et al. Clin. Chem. 2002; 48(8):1305-13 and Plumpton TA, et al. Clinica Chemica Acta 1995; 240:137-54. Since these references were not discussed in the Office Action, nor applied to claims in the application, Applicants need not address them. Applicants' preliminary review of these references indicates that they are not material to their claims, and/or are not prior art. Applicants reserve the right to provide detailed comments on these references at any future appropriate time.

**M. Request for Allowance.**

In view of the above, Applicants respectfully submit that all claims are in condition for allowance, an indication of which is solicited. In the event any outstanding issues remain, Applicants would appreciate the courtesy of a telephone call to the undersigned counsel to resolve any such issues in an expeditious manner and place the application in condition for allowance.

If any fees are necessitated by the filing of this Amendment, please charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,  
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